The Case for Pre- and Peri-conception Measures in the National Children's Study

Prepared by

John Menkedick and Amy Thomas
Battelle

With review and input from

Germaine Buck, Ph.D.,
National Institute of Child Health & Human Development;
Sherry Selevan, Ph.D.,
US EPA National Center for Environmental Assessment; and
Warren Strauss
Battelle

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Recent journal articles and discussions in the research community argue for the inclusion of a preconception cohort in prospective longitudinal studies focused on environmental impacts on children's health. This paper briefly summarizes those arguments as they relate to the National Children's Study (NCS) and identifies the measures proposed as critical to observe prior to the fourth week of pregnancy for NCS-related hypotheses. Measurements prior to the fourth week of pregnancy effectively require recruitment of a preconception cohort, thus resulting in significant cost impacts for the NCS. Such costs need to be weighed in relation to the yield of scientific information generated exclusively by preconception enrollment. As a means of mitigating the costs of a full preconception cohort, the potential for the use of validation sub-sampling in the NCS is briefly introduced and discussed.

As indicated in Table 1, approximately ten of the twenty-one NCS core hypotheses (and one additional hypothesis proposed for inclusion in the NCS) include measures that may be critical to observe prior to the fourth week of pregnancy. These measures fall into three broad categories:

1. Transient exposures (e.g., nonpersistent chemical exposures, indicators of maternal infection or stress), including measures collected from the biological father;
2. Physical/biological measures that are time-dependent, e.g., are affected by physiological changes or behavior modifications during pregnancy such as micro-nutrient levels or physical body measurements; and
3. Other retrospective measures that are subject to recall bias or incomplete or erroneous information, such as estimates of activity patterns or methods used in assisted reproductive technologies (ART).

For NCS hypotheses with potential critical pre- or peri-conception measures, Table 2 summarizes the specific measures and provides comments on their critical nature.

Additional reviews of the literature and conversations with experts suggest that another key reason to include careful measurement of pre- or peri-conception environmentals is for the NCS to serve as a "resource for future studies." The case is made that very early exposures or impacts may have effects on later health. For example, major spatial organization of the body plan begins after implantation (day 7), followed by the critical windows for development of many body organs and systems, beginning as early as the third week of gestation. Exposures during these critical windows are difficult to study retrospectively, which is further complicated by the fact that most women are not aware that they are pregnant until later in pregnancy. The NCS, with its broad health and exposure assessment and collection of archived samples, provides an unusual opportunity to address uncertainty surrounding the impact of these early determinants of children's health (1). Thus, the NCS offers the opportunity to examine, and possibly redefine, critical windows of development. The collection of pre- or peri-conception measures is central to advancing the current state of knowledge concerning the etiology of birth defects and other adverse child outcomes. This assessment has been articulated by the Birth Defects Working Group of the NCS, which has recommended that "the overall study design be based on prepregnancy enrollment because of the importance of looking at exposures during sensitive

periods of development" (2). Other NCS working groups, such as the Fertility and Early Pregnancy Working Group, have suggested the need for a preconception cohort as well.

One important methodology to consider as a possible way to reduce the number of participants sampled preconceptionally is the use of validation sub-sampling. In validation sub-sampling, a representative subset of the cohort is sampled and measured in the most optimal manner possible, in this case by obtaining timely and precise (and costly) pre- and peri-conception measures, which can be referred to as "gold-standard" measures. The entire cohort (including those with the gold-standard measures) receive less costly measurements that are not as timely or precise, but which have some relationship to the gold-standard measures and therefore can serve as "surrogate" measures. By building the relationship between the gold-standard measures and the surrogate measures on those in the representative subset, and using statistical methods to account for measurement error, pre- or peri-conception effects can be studied using the combination of the gold-standard and surrogate measures. The size of the validation subset depends on the expected prevalence of the exposure/outcome and the strength of the relationship between the gold standard measures and the surrogate measures. An example of a gold-standard measure may be the measurement of a pesticide in urine within two weeks of conception. An example of a corresponding surrogate measure might be the measurement of the pesticide metabolite two months post-conception combined with questionnaire data on pesticide use and activity. Further details on the validation sub-sampling approach have been provided at the NCS Sampling Workshop and other forums (3).

Validation sub-sampling is extremely important for preconception measures. Depending on estimates of the adequacy of surrogate measures and the prevalence of exposures and outcomes, validation sub-sampling provides the opportunity to significantly reduce the number of women who must be observed preconception, while still providing sufficient power to estimate the impact of the pre- and peri-conception measures identified in Table 2. If this approach is employed, careful specification of surrogate measures will be an important aspect of planning the NCS.

Table 1. NCS Hypotheses and the Potential Need to Collect Exposure, Physical/Biological, or Other Measures Prior to the 4th Week of Pregnancy

NCS Hypothesis	Transient exposures	Physical/Biological measures	Other measures with retrospective limitations
Current NCS Hypotheses			
NCS Hypothesis 1.1: Among women without diabetes before pregnancy, impaired glucose metabolism during pregnancy is proportional to risk of major congenital malformations of the heart, central nervous system, musculoskeletal system, and all birth defects combined.		✓	✓
NCS Hypothesis 1.2: Intrauterine exposure to mediators of inflammation due to infection of either vaginal, cervical, or uterine sites, or of more distal sites (e.g., periodontal disease) is associated with an increased risk of preterm birth.	✓		✓
NCS Hypothesis 2.1: Repeated low-level exposure to nonpersistent pesticides in utero or postnatally increases risk of poor performance on neurobehavioral and cognitive examinations during infancy and later in childhood, especially, for certain agents, among those with genetically decreased paraoxonase activity.	✓		✓
NCS Hypothesis 2.2: Prenatal infection and mediators of inflammation are risk factors for neurodevelopmental disabilities, such as cerebral palsy and autism.	✓		✓
NCS Hypothesis 2.3: Infection and mediators of inflammation during pregnancy and the perinatal period are associated with increased risk of schizophrenia.	✓		✓
NCS Hypothesis 3.1: Exposures early in life that lead to neurotoxic effects are associated with increased risk of injury.	✓		✓
NCS Hypothesis 3.2: Attributes of childcare and relationship with caregivers influence risk of injury.			
NCS Hypothesis 3.3: Repeated head trauma has a cumulative adverse effect on neurocognitive development.			
NCS Hypothesis 4.1: Exposure to indoor and outdoor air pollution and bioaerosols (including allergens, endotoxin, and mold) is associated with increased risk of asthma.			
NCS Hypothesis 4.2: Respiratory viral infection early in life is associated with increased risk of asthma.			
NCS Hypothesis 4.3: Maternal stress during pregnancy is associated with increased risk of asthma.	✓		✓
NCS Hypothesis 4.4: Antioxidant constituents of diet decrease risk of asthma.		✓	✓
NCS Hypothesis 4.5: Early exposure to bacterial and microbial products decreases risk of asthma (hygiene hypothesis).			
NCS Hypothesis 4.6: Access to health care and management of asthma are strongly related to asthma hospitalization.			
NCS Hypothesis 5.1: Impaired maternal glucose metabolism during pregnancy is directly related to risk of obesity and insulin resistance in offspring.		✓	✓
NCS Hypothesis 5.2: Intrauterine growth restriction as determined by serial ultrasound examination is associated with subsequent risk of central obesity and insulin resistance in offspring, independent of subsequent body mass index.			
NCS Hypothesis 5.3: Breast milk feeding, compared with infant formula feeding, and breastfeeding duration are associated with lower rates of obesity and lower risk of insulin resistance.			
NCS Hypothesis 5.4: Dietary predictors of obesity and insulin resistance include reduced intake of fiber and whole grains, and high glycemic index.			

NCS Hypothesis	Transient exposures	Physical/Biological measures	Other measures with retrospective limitations
NCS Hypothesis 5.5: Environmental factors such as distance to parks, availability of walking routes in the neighborhood, and neighborhood safety are associated with risk of obesity and insulin resistance.			
NCS Hypothesis 5.6: Social, behavioral, and family factors that affect development of dietary preferences and physical activity patterns early in childhood determine risk of childhood obesity and insulin resistance.			
NCS Hypothesis 5.7: In utero and subsequent exposure to environmental agents that affect the endocrine system (bisphenol A, atrazine, and lead) results in altered age at puberty	✓	✓	✓
Proposed Additional NCS Hypotheses			
Gene-environment hypothesis: Exposure to psychosocial stressors during vulnerable periods of pregnancy and early childhood can interact with genotype to permanently alter gene expression related to neurobehavioral outcomes.	✓		
Child maltreatment hypothesis: Marital and/or relationship violence during pregnancy or in the 1st year of the child's life will lead to increased incidence of childhood physical abuse of the child by age 3. Chronic physical abuse will result in altered cortisol levels, increased likelihood of post-traumatic stress disorder, conduct disorder, and oppositional defiant disorder, and impaired developmental functioning. Chronic sexual abuse will result in altered cortisol levels, increased likelihood of post-traumatic stress disorder, and impaired developmental functioning.			
Unintentional injury hypothesis: The relationship between risk taking behaviors of children and parental supervision of children is mediated by environmental (e.g., household hazards) and community (e.g., hazards, park access) factors. Frequency and severity of injuries sustained early in childhood can be used to predict subsequent injuries. Risk taking behavior in children and adolescents is related to the biological reactivity of the individual in infancy. Individuals with increased risk of injury are also at increased risk of other high-risk behaviors such as substance abuse, early initiation of sexual activity, and delinquency.			
Media hypothesis: The amount, type, content and context of media exposure from infancy through adolescence influences brain and neurological development; cognitive and social development, risk behaviors factors related to injury, substance use, sexual health; and obesity and other aspects of physical development. Effects and effect sizes will differ with timing of and cumulative amount of exposure and in different populations with differing vulnerabilities.			
Social environment hypothesis: Eight proposals concerned with the social environment which focus on: families and households; socioeconomic status; neighborhoods and communities; formal institutions; public policy; media; asthma; and obesity.			
Healthy development hypothesis: [*supporting documentation has not been received*]			
Physical/built environment hypothesis: Proposed hypotheses assume a relationship between obesity and physical activity and diet, and focus primarily on identifying predictors of physical activity and dietary habits in relation to built environment.			

Table 2. Specific Measures That May Be Critical to Observe Prior to 4th Week of Pregnancy for NCS-Related Hypotheses

Hypothesis	Potential Critical Pre-4th Week Measure	Comments	Ref
Current NCS Hypotheses			
Among women without diabetes before pregnancy, impaired glucose metabolism during pregnancy is proportional to risk of major congenital malformations of the heart, central nervous system, musculoskeletal system, and all birth defects combined. [**NCS Hypothesis 1.1**] AND Impaired maternal glucose metabolism during pregnancy is directly related to risk of obesity and insulin resistance in offspring. [**NCS Hypothesis 5.1**]	Measures to definitively diagnose preconception diabetes (e.g., glucose tolerance, HgbA1C, blood glucose levels, serum insulin levels, glycemic index, hormones-cortisol)	The issue of how critical a preconception measure of diabetes is depends on the acceptability of the error in retrospective measures of preconception diabetes. Measures of glucose metabolism prior to the 4th week of pregnancy provide information on how glucose metabolism varies over pregnancy.	4
	Micronutrient and other diet and nutrition measures, including: pre-pregnancy weight, BMI, blood pressure, waist-to-hip ratio	Nutritional status during the vulnerable period of fetal development (before 4 weeks) will help determine impact of early nutritional deficiencies or excesses on birth outcomes and will help separate xenobiotic etiologies from nutritional causes. Also important to measure micro-nutrient levels because: physiologic changes during pregnancy complicate determination of micro-nutrient status during pregnancy; and changes in behavior (e.g., changes in physical activity, cessation of smoking and/or drinking alcohol) and use of iron and multivitamin supplements during pregnancy can affect laboratory values.	9
	Medical usage, lifestyle factors, alcohol consumption, smoking status, physical activity measure	The criticality of these measures depends on whether the limitations of retrospective measures are acceptable (e.g., recall bias, incomplete or erroneous information), including limitations of retrospective measures to accurately capture lifestyle changes during the peri-conceptual period.	9
Intrauterine exposure to mediators of inflammation due to infection of either vaginal, cervical, or uterine sites, or of more distal sites is associated with an increased risk of preterm birth [**NCS Hypothesis 1.2**] AND Prenatal infection and mediators of inflammation are risk factors for neurodevelopmental disabilities, such as cerebral palsy and autism [**NCS Hypothesis 2.2**] AND Infection and mediators of inflammation during pregnancy and the perinatal period are associated with increased risk of schizophrenia [**NCS Hypothesis 2.3**]	Measures/indicators of infection (e.g., white blood cell count, vaginal swab for cytokines, hormones-cortisol, medicine usage, recent infection, dental exam) during the first 4 weeks of pregnancy	The criticality of these measures depends on whether the limitations of retrospective measures are acceptable (e.g., recall bias, incomplete or erroneous information)	8, 10

Hypothesis	Potential Critical Pre-4th Week Measure	Comments	Ref
Repeated low-level exposure to nonpersistent pesticides *in utero* or postnatally increases risk of poor performance on neurobehavioral and cognitive examinations during infancy and later in childhood, especially, for certain agents, among those with genetically decreased paraoxonase activity [**NCS Hypothesis 2.1**]	Measures of exposure to nonpersistent pesticides (e.g., phthalates, methoxychlor) during the first 4 weeks of pregnancy	For nonpersistent pesticides with short half-lives, biological samples taken in late pregnancy cannot be considered to accurately represent levels at the time of conception or during early pregnancy.[a] Retrospective exposure information collected by questionnaire is subject to limitations. The criticality of these measures depends on whether the limitations of retrospective measures are acceptable (e.g., recall bias, incomplete or erroneous information)	8, 9, 11, 12
Exposures early in life that lead to neurotoxic effects are associated with increased risk of injury [**NCS Hypothesis 3.1**]	Measures of exposure to nonpersistent neurotoxins or biomarkers of exposure during the first 4 weeks of pregnancy	For xenobiotics with short half-lives, biological samples taken in late pregnancy cannot be considered to accurately represent levels at the time of conception or during early pregnancy.[a] Retrospective exposure information collected by questionnaire is subject to limitations. The criticality of these measures depends on whether the limitations of retrospective measures are acceptable (e.g., recall bias, incomplete or erroneous information)	8, 9, 11, 12
Maternal stress during pregnancy is associated with increased risk of asthma [**NCS Hypothesis 4.3**] AND Antioxidant constituents of diet decrease risk of asthma [**NCS Hypothesis 4.4**]	Diet & nutrition measures, dietary markers	See Hypothesis 1.1. (Assumes nutrition during first 4 weeks is critical for asthma outcome. References?)	9
	Lifestyle factors, smoking status, alcohol consumption	(see Hypothesis 1.1)	9
	Measures of stress (e.g., hormones-cortisol, urine isoprostanes)	Hormones-cortisol is a measure that may change during pregnancy and is expected to be a main explanatory variable since other retrospective measures of stress may be questionable.	9
In utero and subsequent exposure to environmental agents that affect the endocrine system (bisphenol A, atrazine, and lead) results in altered age at puberty [**NCS Hypothesis 5.7**]	Measures of exposure to nonpersistent chemicals during the first 4 weeks of pregnancy	For nonpersistent chemicals with short half-lives, biological samples taken in late pregnancy cannot be considered to accurately represent levels at the time of conception or during early pregnancy.[a] Retrospective exposure information collected by questionnaire is subject to limitations. The criticality of these measures depends on whether the limitations of retrospective measures are acceptable (e.g., recall bias, incomplete or erroneous information).	9, 11
	Dietary assessment	(see Hypothesis 1.1)	
	Medicine usage; environmental tobacco smoke; smoking status; alcohol consumption	(see Hypothesis 1.1)	

Proposed Additional NCS Hypotheses			
Exposure to psychosocial stressors during vulnerable periods of pregnancy and early childhood can interact with genotype to permanently alter gene expression related to neurobehavioral outcomes. **[Gene-environment hypothesis]**	Measures of exposure to psychosocial stressors during "vulnerable periods of pregnancy" (Need clarification on whether this includes measurements during first 4 weeks of pregnancy)	(see Asthma hypotheses above concerning measures of stress)	13
Other NCS-Related Hypotheses			
Resources for future studies (e.g., identifying new associations between exposures and health outcomes)	Exposure and health measurements preconception and during first 4 weeks of pregnancy	During and shortly after conception is a vulnerable period of development during which disruptions (e.g., environmental exposures, nutritional deficiencies or excesses) can affect the health of the embryo. The human reproductive system is forming in the first 4 weeks of pregnancy, and most major organs begin to develop in the embryonic period (3 to 7 weeks) of pregnancy. Disruption of development during this period may result in major physical malformations (congenital anomalies). For example, neural tube defects occur within the first month after conception, and these defects are associated with folic acid deficiency.	9, 12
Assisted reproductive technologies (ART) have health consequences for the offspring	Measures of exposures that occur in conjunction with ART methods (e.g., ovulation drugs, culture media)	Retrospective exposure information is subject to limitations. The criticality of these measures depends on whether the limitations of retrospective measures are acceptable (e.g., recall bias, incomplete or erroneous information)	9
Exposures to environmental agents and medical radiation can injure reproductive germ cells, causing increased incidence of cancer among offspring of the exposed individuals	Measures of pre- and peri-conception exposures (both paternal and maternal), including: benzene, x-rays, ionizing radiation, metals, wood dust, food industry, metal dusts, petroleum products, paints, and pigments	Retrospective exposure information is subject to limitations. The criticality of these measures depends on whether the limitations of retrospective measures are acceptable (e.g., recall bias, incomplete or erroneous information)	5, 8, 9, 12
Environmental exposures impact children's health through sperm DNA via paternally mediated effects	Measures of exposure to environmental toxins; monitoring sperm for abnormalities	Evaluating the DNA quality of sperm after birth of the child have not been successful because sperm are constantly being replenished.	9
Effect of herbal products on human development	Use of herbal products preconception and first 4 weeks of pregnancy	Retrospective information is subject to limitations (e.g., recall bias, incomplete or erroneous information).	7

a Statistical methods that correct for error introduced via temporal variability (or bias) can be used to adjust for this problem if detailed information from a validation subsample, and sufficient sample size, are available.

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